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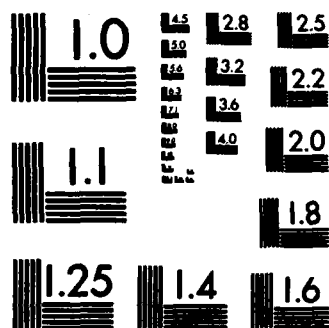
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**THE EFFECT OF PARENTAL METOCLOPRAMIDE, IN CONJUNCTION WITH A
GENERAL ANESTHETIC, ON THE INCIDENCE OF POSTOPERATIVE NAUSEA,
RETCHING AND VOMITING IN AN AMBULATORY SURGICAL SETTING**

A thesis submitted in partial fulfillment of the
requirements for the degree of Master of Science
at Virginia Commonwealth University

By

Kay Ann Prather

B.S.N., Saint Louis University, 1981

R.N., California Lutheran Hospital School of Nursing, 1964

C.R.N.A., United States Air Force School of
Nurse Anesthesia, Wilford Hall, 1978

Director: Salvatore Ciresi, C.R.N.A., M.S.N.
Director of Research Projects
Department of Anesthesia

Virginia Commonwealth University
Richmond, Virginia
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ABSTRACT

THE EFFECT OF PARENTAL METOCLOPRAMIDE, IN CONJUNCTION WITH A GENERAL ANESTHETIC, ON THE INCIDENCE OF POSTOPERATIVE NAUSEA, RETCHING AND VOMITING IN AN AMBULATORY SURGICAL SETTING

Kay Ann Frather, B.S.N.
Medical College of Virginia-
Virginia Commonwealth University, 1983
Major Director: Salvatore Ciresi, C.R.N.A., M.S.N.

Winning (1977:674, 676) stated that "nausea and vomiting are the commonest complications after general anesthesia despite many non-specific prophylactic and therapeutic measures employed to prevent their occurrence." He went on to say that "clearly, therefore, a drug or technique able to reduce postoperative nausea and vomiting to a minimum, would be of great practical use." Metoclopramide is a drug that has central antiemetic effects and additionally speeds gastric emptying. It has minimal side effects. It has been studied as a drug for use in the prevention of postoperative nausea, retching and vomiting with contradictory results. It has not been studied in an outpatient surgical situation where rapid recovery is desirable, and where postoperative problems such as nausea, retching and vomiting must be kept to a minimum.

Thirty patients undergoing minor gynecological surgical procedures in an ambulatory surgery setting were randomly placed in two groups of 15 patients each. The control group was not given metoclopramide in conjunction with their general anesthetic. In the experimental group, five patients received metoclopramide 0.15 mgm/Kg intravenously immediately following intubation; the remaining ten received metoclopramide 0.30 mgm/Kg intravenously during the induction of anesthesia. All patients were preoxygenated for five minutes prior to the induction of anesthesia and were induced using a rapid sequence technique. Sodium brevitall 1 mgm/Kg, d-tubocurarine 0.04 mgm/Kg and succinylcholine

1.5 mgm/Kg body weight were the induction agents. Maintenance of anesthesia was accomplished using fentanyl 2 ug/Kg intravenously and 70 percent nitrous oxide with 30 percent oxygen. Isoflurane, at a maximum of one percent, was added when needed. A succinylcholine (0.2 percent) drip was utilized for relaxation as necessary.

→ Patients were observed during their recovery room stay, until their discharge, for the incidence of nausea, retching and vomiting using a tool designed for this purpose. Twenty-four hours later they were contacted by phone and questioned concerning the occurrence of nausea, retching and vomiting experienced after their discharge home.

↘ Comparing the drug-treated subjects with those receiving no drug, there was no significant difference in the occurrence of any of the symptoms--nausea, retching or vomiting in either the recovery room or at the 24-hour point. In only one case was there even a marginally significant difference in the occurrence of a symptom (if $p=0.05$) and that was for vomiting. When looking at the treatment groups in comparing their effects at both the recovery room and 24-hour time frames, vomiting did occur marginally less than the other two symptoms in this case when looking at both treatment regimes and time frames ($p=0.0585$). ↗

CHAPTER 1

CONCEPTUAL FRAMEWORK

Introduction

"There is perhaps no more frequent sign or symptom of illness than nausea and vomiting." (Matthieson, 1978:109) Etiologies for the symptoms of nausea and vomiting are multiple, and a complete list would include (among others) pain, disease processes, infection and anesthesia. Nausea and vomiting are usually mild and self-limiting; but if vomiting should persist, electrolyte imbalance, dehydration, aspiration and alkalosis are possible complications—all frequently accompanied by considerable personal distress. The final result may be the precipitation of further vomiting. Choosing whether to use an antiemetic for either the prevention or treatment of nausea and vomiting must be thoughtfully considered, benefits being weighed against possible risks, the final choice being firmly supported by pharmacological, physiological and clinical considerations. (Hoover, 1970) (Bank, 1976) (Matthieson, 1978)

Postoperative nausea, retching and vomiting, and their causes, have always been of concern to the anesthetist. There have been multiple studies dealing with these problems; and all seem to validate the supposition that nausea, retching and vomiting are indeed postoperative problems with which the anesthetist must deal, but there is considerable disagreement as to their importance.

Knapp (1956) and Dundee (1965) chose to deal with the issue from the patient's point of view noting that, to the individual undergoing surgery, the postoperative period was most dreaded because of its association with the experience of nausea and vomiting. Furthermore, the individual often attributed these symptoms to the anesthetic experience itself. Bonica (1958:532) stated that "despite improvements in anesthetic experience and agents, the almost

demoralizing symptoms of nausea, retching and vomiting still occur with sufficient frequency as to constitute, from the patients' viewpoint at least, the most important complications of surgical and obstetrical anesthesia."

Belleville (1961) reported that in his studies, as well as in those of others, there was a decrease in postoperative nausea and vomiting as compared to studies published a decade before which frequently reported figures in excess of 50 percent. He expressed the belief that varying results in such studies reflect "differences in criteria used to define nausea and vomiting, in the length of time patients were followed, in the closeness of observation, in the techniques employed for anesthesia, and in the patient population." (Belleville 1961:773) A few of the factors which he and other authors have identified as contributors to the incidence of nausea and vomiting include duration and type of anesthetic (the longer the anesthetic, the more likely nausea and vomiting will occur postoperatively), the sex of the patient (women showing as much as a threefold incidence of nausea and vomiting when compared to men), whether a narcotic was used as a premedication (its usage increased the likelihood of nausea and vomiting), and the operative site (some saying intraperitoneal procedures show an increase in postoperative nausea and vomiting, and others being unable to confirm this finding). (Dent, 1955) (Bonica, 1958) (Smessaert, 1959) (Dundee, 1965) (Wylie, 1972) (Winning, 1977)

Adriani (1961:666) asserted that "vomiting being inevitable after inhalation anesthesia is so ingrained in the minds of patients and doctors alike that it is virtually accepted as fact." The study which accompanied this statement was conducted in order to evaluate the "true" incidence of vomiting (nausea was not studied because of its subjective nature), categorizing it as transitory or intractable and therefore requiring treatment. If an antiemetic was used, its effectiveness was also evaluated. Results of this study set the overall incidence

of vomiting at 23 percent (n=2,230). Severe vomiting requiring treatment occurred in only 3.5 percent of the cases studied. Antiemetics, when used, were effective in the reduction of vomiting, but their side effects were not always acceptable (for example, hypotension).

Figures vary then, depending on inherent variables (anesthetics used, sex, preoperative medication given, etc.), but the overall incidence of nausea and vomiting lays somewhere within a range of 30-68 percent of all surgical patients, with a three to five percent range for persistent vomiting which required an antiemetic for control. (Dent, 1955) (Smessaert, 1959) (Belleville, 1961) (Matthieson, 1978) (Mortensen, 1982)

Since the incidence of nausea and vomiting was rarely predictable and frequently variable, and because antiemetics were often associated with undesirable side effects, it was not surprising that the majority of authors reviewed were of the opinion that the prophylactic, routine use of an antiemetic was unjustifiable. (Knapp, 1956) (Keats, 1960) (Belleville, 1961) (Andriani, 1961) (Wyllie, 1972) (Collins, 1976) (Stoelting, 1981)

The fact remains, however, that nausea and vomiting continue to be frequently encountered postoperative problems. As Winning (1977:674) stated, "nausea and vomiting are the commonest complications after general anesthesia despite many nonspecific prophylactic and therapeutic measures employed to prevent their occurrence." Mortensen (1982:51) agreed with this statement, adding that "nausea and vomiting in connection with general anesthesia are possibly considered by some investigators as of little real interest, since they rarely give rise to serious complications. . . Many patients, however, consider nausea and vomiting very distressing." Both authors noted the wide ranges of incidences reported and agreed that the subject should be given continued study. Both felt that prophylactic treatment needed to be considered in some cases. Winning

(1977:676) summarized the problem with the statement that "clearly, therefore, a drug or technique able to reduce postoperative nausea and vomiting to a minimum would be of great practical use." His statement succinctly expressed the premise upon which this study was based.

Metoclopramide is a drug that was developed by French investigators in 1953. It has antiemetic effects that have been studied in a variety of situations, including the postoperative period. Results are contradictory and there are no studies dealing with the outpatient surgical population. Since metoclopramide is a relatively short-acting drug with few side effects, it may be especially suited for use in outpatient surgery anesthetic techniques.

Nausea, Retching and Vomiting

There are numerous factors which can affect the incidence of postoperative nausea, retching and vomiting. These may include sex, anesthetic agents, whether a premedication was used, age, and the type of surgical procedure. The individual roles of these factors in producing nausea, retching and vomiting is difficult to establish—especially since a particular factor (for example, duration of surgery) may not play an adverse role in all circumstances. (Knapp, 1956) (Burtles, 1957) (Wylie, 1972) (Riding, 1975) Knapp (1956:376) describes postoperative sickness as "the troublesome triad of symptoms—nausea, vomiting and retching." Retching is synonymous with vomiting when the muscular responses that are occurring are compared, but in retching gastric contents are not expressed as they are in vomiting.

This triad of symptoms represents a complex response of the body requiring careful coordination and timing of somatic as well as visceral components. Afferent impulses leading to the reflex of vomiting can arise from many sources. Such impulses proceed to the central nervous system through vagal and sympathetic

pathways. Integration of these afferent impulses occurs within the brain stem, specifically in the bilateral vomiting centers. These centers lie within the reticular formation of the medulla at the level of the olivary nuclei. The motor responses associated with vomiting and retching are initiated in the vomiting center, leaving the central nervous system through the fifth, seventh, ninth, tenth, and twelfth cranial nerves traveling to the upper gastrointestinal tract, and through the spinal nerves traveling to the diaphragm and abdominal muscles. Vomiting represents a highly integrated event of the respiratory and somatic nervous systems, and not of the gastrointestinal tract. (Cummins, 1958) (Guyton, 1976) (Ganong, 1977)

Vomiting usually begins with salivation and the sensation of nausea. Nausea is the conscious recognition of the subconscious excitation of an area of the medulla closely associated with or a part of the vomiting center. It can be caused by irritative impulses from the gastrointestinal tract, impulses in the brain associated with motion sickness, or impulses from the cortex, all of which can initiate vomiting. (Guyton, 1976) It is accompanied by interruption of gastric contractions, decreased gastric tonus, reduced acid output, mucosal pallor and an acceleration in the production of mucus. These gastric phenomena seem to be clearly the result and not the cause of nausea as persons who have had total gastrectomies are able to experience nausea. (Cummins, 1958)

A common cause of nausea is distention or irritation of the duodenum or lower small intestine causing it to contract forcefully while the stomach relaxes allowing intestinal contents to reflux into the stomach. This is preliminary to the vomiting that frequently follows. Vomiting can occur without nausea—an indication that only portions of the vomiting centers are associated with the sensation of nausea. (Guyton, 1976)

In the vomiting act, the glottis is closed (preventing aspiration of vomitus into the trachea), the breath is held at mid-inspiration, and the abdominal muscles

and diaphragm contract. Because the chest is held in a fixed position, intra-abdominal pressure increases, esophageal and gastric cardiac sphincters relax, and reverse peristalsis begins with gastric contents being ejected. (Ganong, 1977) (Newman, 1980)

The chemoreceptor zone also plays a part in the vomiting reflex. This zone is located in the area postrema, a V-shaped band of tissue on the floor of the fourth ventricle near the obex. It contains clusters of large cells surrounded by a prominent capillary network and bundles of nerve fibers arising from smaller cells and is an area showing increased permeability for many substances when compared to other parts of the medulla. The large cells are sensitive to emetics in the circulating blood; the small cells serve to conduct impulses for initiating the vomiting reflex to the vomiting center. Lesions of this area have little effect on vomiting initiated through gastrointestinal irritations but abolish vomiting after injection of apomorphine or other emetic drugs. (Ganong, 1977) (Newman, 1980)

Metoclopramide

Metoclopramide was developed in France by investigators of the Delegrange Laboratories. Its discovery was an outgrowth of a systematic study of the chlorinated derivatives of para-aminobenzoic and para-aminosalicylic acids. It is related to procaine, a local anesthetic known to have slight antiemetic effects. The original drug, orthochloroprocainamide, was synthesized by Justin-Besancon and associates in 1953. In 1957, Besancon discovered its antiemetic properties which were uniquely devoid of the accompanying depressant action on the central and autonomic nervous systems characteristic of the phenothiazine group of antiemetics. In addition, he and his associates discovered that the drug caused an acceleration of gastric emptying time and decreased intestinal transit time.

These findings were considered to be a "bonus." It was postulated that these findings could lead to special applications in clinical settings where the threat of aspiration was a concern (emergency surgery, labor and delivery). (Klein, 1968) (Schulze-Delrieu, 1979 and 1981)

Within the brain, metoclopramide seems to work on the dorsal and ambiguous nucleus of the vagus nerve, the vomiting center, and the chemoreceptor trigger zone. All of its effects seem to occur through dopaminergic antagonism. Metoclopramide increases dopamine turnover time and appears to work on post-synaptic dopamine receptors. As was addressed earlier, the vomiting center responds to afferent impulses arising in the gastrointestinal tract and in the chemoreceptor trigger zone. Nausea and vomiting are the responses elicited. Metoclopramide decreases the number of impulses reaching the vomiting center from these two areas and may elevate the threshold level of the chemoreceptor trigger zone. (Pinder, 1976) (Jenner, 1979) (Schulze-Delrieu, 1981)

The multiplicity of actions which metoclopramide has on the gastrointestinal tract contrasts sharply with its apparently pure antidopaminergic effects within the central nervous system. It has been shown to block the activity of dopamine on the tissues of the alimentary canal, but many of these peripheral effects can be explained by alternative mechanisms. The effect metoclopramide produces on the gastrointestinal tract includes an increase in resting muscle tension--especially of the lower esophageal sphincter and the gastric fundus. It also increases peristalsis in the gastric antrum and small intestine with an increased coordination of muscular activity of various gut segments, exemplified by relaxation of the pylorus and duodenum during the stomach contraction. Its effect on the colon is minimal. (Pinder, 1976) (Schulze-Delrieu, 1979 and 1981)

In the stomach, immobility, dilatation and reverse motility accompany the vomiting reflex. Metoclopramide prevents immobility produced by small doses of

apomorphine and seems to reinforce aboral motility of the gut. (Schulze-Delrieu, 1981)

Metoclopramide exhibits few side effects of any consequence. Its extrapyramidal side effects are the most alarming, but these occur in only one percent of patients studied and are usually confined to females and young adults. They consist of dystonic-type reactions and can include torticollis, trismus, and facial spasms, resembling the dyskinesias induced by the phenothiazides. Severe cases respond readily to treatment with bntropine or diazepam. Other side effects that have been observed include drowsiness, lassitude, bowel disturbances, dizziness, and faintness. All clear when the drug is withdrawn. (Pinder, 1976) (Schulze-Delrieu, 1979 and 1981)

Metoclopramide is weakly bound to serum proteins and is rapidly and widely distributed in most tissues. It can be given orally, intramuscularly, and intravenously. Maximal plasma levels occur within 30 to 120 minutes when it is given orally. Its plasma half life is short, ranging from one to four hours. In the central nervous system its distribution is localized to the area of the postrema where the chemoreceptor zone is located. Within 24 hours, about 80 percent of it is excreted unchanged in the urine, or as the sulfur and glucuronide conjugates of the nonmetabolized drug. It is a comparatively safe drug, and overdoses in the magnitude of 100 times its recommended dose have been tolerated without serious side effects. (Pinder, 1976) (Schulze-Delrieu, 1979 and 1981)

Problem Statement

Nausea, retching and vomiting continue to be frequently encountered postoperative events. Though some authors do not consider them as true complications they can be responsible for causing the postoperative patient considerable distress; and in the extreme case where intractable vomiting occurs may result in other complications, thus prolonging the convalescent period. As

an anesthetist, this investigator believes that the search for an antiemetic particularly suited for the needs of the postoperative patient should be continued in order to increase patient comfort, to reduce the incidence of nausea, retching and vomiting, and to help assure early discharge—an essential in outpatient surgery, the situation in which this study was conducted.

The purpose of this study was to determine if the administration of parental metoclopramide, in conjunction with a general anesthetic, affected the incidence of nausea, retching and vomiting in the postoperative period.

Definition of Terms

1. Nausea: A subjective sensation that can be described as the desire to vomit without the accompanying expulsive movements. As nausea increases in severity, objective signs may appear—including increases in heart rate, blood pressure, salivation and swallowing. Respirations may become deeper and assume a spasmodic pattern. Vasomotor disturbances with pallor and sweating may become evident. (Knapp, 1956) (Bonica, 1958) (Matthieson, 1978)
2. Vomiting: The act of forceful expulsion of the gastrointestinal contents through the mouth. It is distinguished from retching by the production of gastric contents. Retching usually indicates an empty stomach. (Knapp, 1956) (Bonica, 1958) (Matthieson, 1978)
3. Metoclopramide, 4-amino-5-chloro-2-methoxy-N-(2-diethyl-aminoethyl)benzamide: A drug structurally related to procainamide which possesses a potent antiemetic effect, apparently through direct action on the chemoreceptor zone in the floor of the fourth ventricle, bilaterally.
4. Parental Administration: The route utilized in this study for the administration of the metoclopramide was direct intravenous injection.

5. Induction: The process through which the state of general anesthesia is achieved.
6. Rapid Sequence Induction: A technique consisting of preoxygenation, a head-up tilt position and Sellicks' maneuver followed by the administration of a rapid-acting barbituate and a muscle relaxant. Ventilation is not assisted. Intubation is performed with cuff inflation being accomplished prior to assisting patient ventilation.
7. General Anesthesia: "An irregular descending depression of the entire nervous system . . . in which certain physiologic systems of the body are brought under a condition of external regulation by the action of various chemical agents." (Collins, 1976:225) Sufficient blood concentrations of these agents must be achieved so that unconsciousness results. These agents may be administered by a variety of routes (examples: intravenous, inhalation, rectally).
8. Postoperative Period: That period following surgery. In this study it was limited to the first 24 hours after surgery.
9. American Society of Anesthesiology Classification (Collins, 1976): A grading system designed to define the physical status of a patient. Specifically, it refers to the medical condition of the patient and to the overall efficiency and function of his organ systems. It does not connote his total operative risk. In this study, all patients were either A.S.A. Class I or II:
I - No disease other than surgical pathology; no systemic disease.
II - Moderate systemic disturbance due to general disease or surgical condition.
10. Patient: A healthy female, A.S.A., Class I or II, between the ages of 18 and 45, undergoing an elective, minor gynecological surgical procedure (diagnostic laparoscopy, laparoscopy for tubal ligation, or breast biopsy) in

the ambulatory surgery clinic of a hospital in the Atlantic Southeast under general anesthesia with endotracheal intubation.

11. Control Group: That group of patients who did not receive metoclopramide, nor any other antiemetic type of medication as part of their anesthetic management.
12. Experimental Group: That group of patients who did receive metoclopramide (either 0.15 mgm/Kg or 0.30 mgm/Kg of body weight as part of their general anesthetic management).

Hypothesis

The parental administration of metoclopramide in conjunction with a general anesthetic will result in a decreased incidence of postoperative nausea, retching and vomiting.

Variables

Dependent: Postoperative nausea, retching and vomiting.

Independent: Parental administration of metoclopramide.

Assumptions

1. Patients included in this study arrived for surgery in a fasting state having had nothing to eat or drink since the midnight prior to the morning of surgery.
2. The tool utilized in this study had been adequately explained to the recovery room personnel before being asked to use it.
3. Patients were observed adequately in the recovery room for the occurrence of nausea, retching and vomiting, and such observations were recorded on the tool provided.

4. Patients that participated in the study understood the terms nausea, retching and vomiting as defined by this study.
5. Patients answered questions about whether they had experienced nausea, retching and/or vomiting in the postoperative period, truthfully, when contacted at the 24-hour point by phone.

Limitations

1. Nausea is subjective sensation and, as such, individual perception of its occurrence or severity may vary.
2. The results obtained in the selective population being studied may not be generalizable to a heterogenous population inclusive of all adults.
3. Since individuals in this study were outpatients and follow-up at the 24-hour point was conducted through telephone contact, some of the population was lost through the inability to reach an individual in the time frame specified.
4. Individuals differ in their drug responses, drug metabolism and drug sensitivity. Such individual differences were not identifiable within the framework of this study.

Delimitations

1. The amount of d-tubocurarine given as a defasciculation dose was 0.04 mgm/Kg of body weight, intravenously.
2. The amount of succinylcholine given intravenously to relax the patient for intubation was 1.5 mgm/Kg of body weight.
3. The dose of sodium brevitall given intravenously during the induction process was 1 mgm/Kg of body weight.
4. The amount of metoclopramide given intravenously in conjunction of general anesthesia was either 0.15 mgm/Kg or 0.30 mgm/Kg of body weight.

5. Induction of anesthesia was through a rapid sequence technique preceded by three to five minutes of preoxygenation to decrease the introduction of air into the stomach.
6. Maintenance of anesthesia was accomplished with fentanyl 2 ug/Kg of body weight given intravenously and 70 percent nitrous oxide with 30 percent oxygen. Isoflurane to a maximum of one percent was added as needed.
7. Muscle relaxation was obtained through the use of an 0.2 percent succinylcholine drip and did not exceed 7 mgm/Kg.

Research Design

The research design for this study was quasi-experimental. Quasi-experimental designs are much like experimental designs except that one of the three properties characteristic of a true experimental design (manipulation, control or randomization) is missing. The missing property is always either control or randomization, or may be both; manipulation of an independent variable through institution of a treatment is always present. (Polit, 1978) This approach was chosen since random selection of the population was not desired. Rather, a particular segment of the population with certain characteristics (healthy female patients, A.S.A. Class I or II undergoing minor gynecological procedures) and in a particular setting (ambulatory surgery) was purposely selected for study. These restrictions allowed the drug metoclopramide to be studied in the "normal" patient in a surgical setting where it had not previously been studied.

There are four limitations to be addressed in this study. The limitations are: (1) the subjective nature of the symptom nausea, (2) the inability of the study to be generalizable to a heterogenous population inclusive of all adults, (3) the potential of losing data which would occur in the event of the inability to reach a patient by phone at the 24-hour point after surgery, and (4) the individuality of patients in their response to drugs.

Since nausea is a subjective symptom perceived by individuals differently and is not a verifiable event, it is a difficult symptom to validate (Adriani, 1961). Regardless, nausea can be unpleasant and very distressing for the individual experiencing it. (Mortensen, 1982) Nausea frequently accompanies episodes of retching and vomiting in the postoperative period or may be the only symptom of the triad experienced. For these reasons, it was included in the symptomatology studied.

Since the gynecological surgical procedures that the patients in this study underwent are performed with some frequency and represent a high percentage of procedures done in the outpatient surgical setting, this population was chosen because of its accessibility and because of the high incidence of nausea and vomiting seen in female patients. (Belleville, 1961) Though not generalizable to a heterogenous population inclusive of all adults, the results could be applied and further studied in the special situation in which this study was done.

One patient was lost when attempts to reach her in the follow-up call at the 24-hour point were unsuccessful. This limitation was beyond the control of the investigator.

The individuality of patient response to drug therapy is probably inherent in any study undertaken where drugs are utilized. Variation deals with the difference in magnitude of response occurring among individuals within a population given the same dose of a drug. Goodman and Gilman (1980:37) state that "even when all known sources of variation are controlled or taken into account, drug effects are never identical in all patients or even in a given patient on different occasions. A dose effect curve applies only to a single individual at one time or to the average individual."

The delimitations involved in this study are listed and discussed elsewhere in this paper. The doses utilized and listed in the delimitations were those conforming to current anesthesia practice standards. (Collins, 1976)

According to Polit and Hungler (1978), there are a number of threats to the internal validity of a quasi-experimental design. Internal validity refers to the extent to which it is possible to make inference that the experimental manipulation present in a study resulted in any observed difference. The threats include history, selection, maturation, testing, and mortality.

History deals with external events taking place concurrently with the treatment which could affect the variables of interest. In this study, history was essentially disregarded since patients were normal and in a controlled environment.

Selection encompasses bias resulting from pre-treatment differences between the experimental and control groups when individuals are not randomly assigned to those groups. The possibility then exists that the two groups are not equivalent. The population involved in this study was randomly placed in either the control or experimental groups using a randomization table prepared for the study, after permission for inclusion into the study had been obtained from the subjects.

Maturation refers to processes that are occurring within the subjects during the course of the study that were the result of time rather than treatment. Maturation effects in this study were negligible since the time period involved was no more than 36 hours considering that time to encompass the patient's arrival in the ambulatory surgical setting through the time of phone contact the day after surgery.

Testing, or the effect of taking a pre-test on the post-test results, is not relevant since there was no pre-test.

The final threat, mortality, refers to the differential loss of subjects from comparison groups during a study and is termed attrition. Mortality occurred when subjects were not successfully reached at the 24-hour point by phone and has already been taken into account under limitations. There was a loss of one subject through mortality in this study.

External validity is the ability to generalize research findings of a study to other settings. Potential threats to external validity include the Hawthorne effect, novelty effects, experimental effects, and measurements effects. (Polit, 1978)

The Hawthorne effect refers to the fact that subjects may behave in a particular manner largely because they are aware of their participation in a study. Because the symptomatology being examined by this investigator was never specifically referred to either in the explanation of the study or at any time during collection of the data, this effect was probably eliminated. Subjects were aware of the interest in their recovery but were unaware of what particular aspects or observations were being noted. During the call at the 24-hour period, subjects were encouraged to vocalize any recovery problems they may have experienced after discharge from the ambulatory service. Only after this, if they had not voiced any of the three symptoms, were they asked directly if they had suffered from any of the three during their recovery.

Novelty effects refer to the way in which researcher and subject alike might alter their behavior when a new treatment is being utilized. The subjects, as addressed above, were not aware of the behavior for which they were being observed. In the recovery room and during the phone contact, the subjective symptom (nausea) was not referred to until the subject had been given the opportunity to voice its occurrence himself. Also, because retching and vomiting are objective symptoms and easily recognized, this effect was minimized.

Interaction of history and treatment effects addresses the impact that other events external to the study may have on the study's results. Because of the controlled environment and the "normal" subjects, this effect was not considered to be problematic.

Experimental effects addresses the communication of researcher expectations (the emotional and intellectual investment of the researcher in his study to

demonstrate that his hypothesis is correct) to the subjects (thus altering their response). It also involves the bias that may occur in the researcher's observations during data collection secondary to his expectations. The wording of the explanation and the technique used on the recovery room tool and on the follow-up phone call were purposely designed to minimize this problem.

Measurement effects deals with the problem of generalizing the results of a study to another group of people not exposed to the same data collection procedures. This is a realistic problem and one that has been present in probably all studies interested in the symptomatology involved here and no doubt accounts, in part, for the wide variations in the incidences reported for these symptoms in previous studies looking at the postoperative period. (Belleville, 1961)

CHAPTER 2

LITERATURE REVIEW

Metoclopramide has been subjected to therapeutic clinical trials in a wide variety of dysfunctions. Discussion here will primarily deal with its antiemetic effects in the postoperative patient. Studies able to demonstrate its effectiveness, as well as those unable to confirm its effectiveness in this situation will be addressed. The first study is the exception. It deals with the use of metoclopramide against apomorphine-induced nausea and vomiting. Apomorphine seems to induce nausea and vomiting through the same mechanisms as narcotics. Since narcotics are frequently utilized in anesthesia, both preoperatively and intraoperatively, and were used intraoperatively during this research thesis, this study is of particular interest.

Klein (1968) designed a study to determine the effectiveness and duration of action of metoclopramide in protecting against apomorphine-induced vomiting and to compare it to two other antiemetics--trimethobenzamide and prochlorperazine. Metoclopramide is known to work centrally at the chemoreceptor trigger zone (antiemetic effect). Apomorphine and narcotics such as morphine sulfate and meperidine ("pethidine") which are used with some frequency in anesthesia, as well as pre- and postoperatively, also work centrally at the chemoreceptor trigger zone (emetic effect).

The population consisted of a volunteer group of 58 healthy male prisoners. Apomorphine was given intravenously one to two hours after a regular meal or 30 minutes after a test meal on a weekly basis, beginning at ten micrograms per kilogram and increasing by ten micrograms per kilogram each week until vomiting consistently occurred. This dosage was termed the TED (threshold emetic dose). Testing continued on a weekly basis thereafter, and again the apomorphine dose

was increased by 10 mgm/Kg each week, but volunteers were first given either metoclopramide, trimethobenzamide, or prochlorperazine before beginning the intravenous apomorphine. Metoclopramide was given either orally (20 mgm; nine subjects), rectally (20 mgm, ten subjects), or intramuscularly (0.15 mgm/Kg, seven subjects; 0.30 mgm/Kg, ten subjects). Trimethobenzamide was given intramuscularly (3 mgm/Kg, seven subjects) as was prochlorperazine (0.15 mgm/Kg, seven subjects). An additional eight subjects received an oral placebo. The intramuscular doses of metoclopramide markedly increased the TED of apomorphine (three to five times) as did the oral and rectal doses. Its effect extended up to 24 hours in some cases. There were no significant differences between the three routes. Metoclopramide was as effective as a similar dose of prochlorperazine, and both metoclopramide and prochlorperazine were superior to trimethobenzamide in their antiemetic effects. Placebo offered no protection beyond the TED.

One of the earlier studies done to investigate the effect of metoclopramide on postoperative nausea and vomiting was performed by Handley in 1967. His study was a double-blind study, comparing metoclopramide to the "established" antiemetic, perphenazine. He investigated 65 healthy women, all under 60 years of age, undergoing dilatation and curettage, or dilatation only. All received papavatum and atropine as preoperative medications, were induced with sodium thiopental, and were administered general anesthesia by mask utilizing nitrous oxide, oxygen and halothane. The women were given either metoclopramide 10 mgm (26), perphenazine 5 mgm (24), or normal saline 1 cc, intramuscularly, at the end of the surgical procedure. Oral intake was limited to sips of water for at least four hours postoperatively. The events of nausea and vomiting, their severity, and the time they occurred were recorded during the postoperative period by nurses instructed in the observations to be made. The investigators questioned each patient as a follow-up to confirm the recorded events. Degrees

of severity for nausea and vomiting were to be included in the notations, but subjectivity became too much of a limiting factor and final classifications included: no nausea and vomiting; nausea but no vomiting; and, vomiting--the latter two being combined for statistical purposes. Both metoclopramide and perphenazine were found to be more effective in prevention of postoperative nausea and vomiting than placebo alone. When the two drugs were compared, there was no statistical difference found between the two.

Another study in 1968 by Dobkin, et al., was run to compare the effects of metoclopramide (20 mgm), trimethobenzamide (300 mgm), and a placebo, on postanesthetic nausea and vomiting. All three drugs were given randomly as a single intravenous dose 30 minutes before the end of the operative procedure. The surgeries were all elective upper-abdominal procedures performed on 284 adult patients. The anesthetic agents were standardized (sodium thiopenthal for induction, gallamine for intubation, and maintenance with methoxyflurane, nitrous oxide and oxygen). It was known that when methoxyflurane is used as a primary anesthetic and there are no preventative measures taken, there is a 40 percent incidence of nausea, retching and vomiting. A nasogastric tube was placed in two thirds of the patients for postoperative use. Patients were observed for nausea and vomiting the first six hours postoperatively, and events were recorded by the nurse making the observations. Charts were reviewed after 24 hours for the incidence of the symptoms. The identity of the compounds was not revealed until the study was completed and data had been keypunched for analysis. Results showed that neither metoclopramide nor trimethobenzamide were better than placebo with respect to nausea and vomiting during the first 24 hours in patients without a nasogastric tube. For patients with nasogastric suction, there was at least a 50 percent lower incidence of nausea and vomiting, especially prominent in patients treated with metoclopramide. At least one third

of the patients who developed nausea and vomiting did so after receiving a narcotic. On the basis of this study, neither drug was significantly effective in reducing postoperative nausea and vomiting.

Clark and Storrs (1969) studied 100 women, ages 18-44, requiring general anesthesia for the evacuation of the uterus after incomplete abortion. Half of the women received 20 mgm of metoclopramide, intramuscularly, on arrival in the recovery room; the other half received 2 cc of saline, intramuscularly, administered in a double-blind fashion. Preoperative medication was a combination of morphine (10 mgm), and atropine. Sodium thiopentothal was used for induction, and maintenance of anesthesia was by mask using low concentrations of trichloroethylene, nitrous oxide, and oxygen, with spontaneous ventilation. In no case was there vomiting on emergence. Interview was conducted in a casual fashion on the following day with the assessment of nausea and vomiting being of prime interest. Identity of the drug which the patient had received was not known by interviewers until the study was completed. The incidence of nausea and vomiting in patients treated with metoclopramide was less than in those receiving placebo. Nausea was not significantly reduced, but vomiting was significantly reduced in those patients treated with metoclopramide. Food and drink were given freely in the postoperative period, and assessments noted on the records were based on recall and nursing observations.

Also in 1969, Tornetta reported the results of a study which he had conducted over a three-year period with observations of more than 600 cases. The study consisted of four parts and was concerned with the evaluation of the efficacy and safety of metoclopramide when used for prevention of postoperative nausea and vomiting. Part one studied 283 adults undergoing elective surgery. A single intramuscular dose of 10 mgm of metoclopramide was given to 145 patients ten minutes prior to the expected termination of surgery; the other 138 patients

received a placebo. The medications were given in a double-blind fashion. The occurrence of nausea, retching and vomiting were observed and recorded for at least four hours postoperatively. There were statistically significant differences favoring metoclopramide when considering nausea, and/or vomiting ($p>0.005$), nausea alone ($p>0.0125$), or when considering vomiting alone ($p>0.005$).

Part two of Tornetta's study dealt with the effect of metoclopramide on vital signs and will not be considered here.

Part three was a comparative evaluation of 300 postsurgical patients selected because they offered a high risk of nausea and vomiting. The patients were randomly divided into three groups of 100—the first group receiving 20 mgm of metoclopramide intramuscularly, the second receiving 10 mgm prochlorperazine intramuscularly, and the third receiving a placebo intramuscularly—all administered as a single 2 cc dose just prior to emergence from anesthesia. Preoperative medication consisted of a narcotic plus scopolamine or atropine, atropine alone, or pentobarbital and scopolamine. Observations were continued for four hours after emergence from anesthesia and included notations concerning the incidence of nausea, retching and vomiting. The incidence of the symptoms was significantly less in the metoclopramide ($p<0.001$) and prochlorperazine ($p<0.01$) groups when compared with the placebo group. Nausea and vomiting were more frequently seen in those over the age of 40 or in those who had had intraabdominal procedures.

Part four of his study evaluated the therapeutic effects of metoclopramide in 45 patients who experienced severe postoperative nausea and/or vomiting. Most were between the ages of 25 and 45, and 22 had had intraabdominal procedures. Only patients with severe nausea who had vomited at least twice were included in this group. Thirty-five of the patients received 10-60 mgm of metoclopramide intramuscularly, nine received 25-50 mgm in 500 or 1,000 cc of

five percent dextrose in water by intravenous drip (average duration: seven hours), and one patient received 10 mgm of metoclopramide intramuscularly combined with 20 mgm by intravenous drop. Antiemetic protection was achieved for more than four hours in 28 of the 35 patients who received either one or more intramuscular doses of metoclopramide. Of those receiving intravenous metoclopramide, nausea and vomiting was completely controlled in eight patients, and in two others relief occurred only while the drip was running.

Tornetta concluded that metoclopramide was both a potent and effective antiemetic agent comparable to prochlorperazine for both the prophylaxis and treatment of the symptoms of postoperative nausea and vomiting. He noted that metoclopramide was without serious side effects. He went on to recommend that further study of the drug should be accomplished.

Breivik and Lind conducted two studies involving the use of metoclopramide. The 1970 study compared the preventative effects of metoclopramide and perphenazine on postoperative nausea and vomiting in a population of otherwise healthy women (188) undergoing gynecological laparotomies. The premedication (contained a narcotic) and anesthetic techniques were identical in all cases. The metoclopramide (10 mgm) and perphenazine (5 mgm) were administered intramuscularly at the end of surgery from vials that were identical and had been coded through randomization. Patients were followed for six hours in the recovery room—observations being made every half hour to evaluate the occurrence of nausea, vomiting and retching. Each patient received a "nausea score" based on these observations—a low score indicating a better antiemetic effect than a high score. Pithidine was given intramuscularly as needed for pain. The group treated with metoclopramide demonstrated significantly less nausea, retching and vomiting than the perphenazine-treated group. In the group treated with metoclopramide, 41 percent needed pithidine in the first six hours; in the perphenazine group, 65

percent required pithidine. Excluding these individuals, the incidence of retching and vomiting was 14.3 percent in the metoclopramide group, compared to 39.5 percent in the perphenazine-treated group--a statistically significant difference.

In their 1971 study, Breivik and Lind utilized a group of 60 female patients, between the ages of 20 and 69 years undergoing non-complicated cholecystectomies. Thirty of the women received 10 mgm of metoclopramide intramuscularly, and 30 received a placebo intramuscularly administered in a double-blind fashion. Four doses of each were used--doses being given at the end of operation, at 8:00 in the evening the day of surgery, and at 7:00 in the morning and 2:00 in the afternoon on the first postoperative day. All patients were premedicated preoperatively with pithidine 75 mgm and atropine 0.6 mgm. Induction of anesthesia was accomplished with sodium thiopental and succinylcholine followed by intubation. Halothane and nitrous oxide with oxygen were employed for anesthetic maintenance with alcuronium utilized for relaxation. Pithidine 50 to 75 mgm was given for postoperative pain relief. Nausea, retching and vomiting were recorded for the first six hours in the recovery room using the "nausea score" as described in the 1970 study. For the next 12 hours patients were observed for retching and vomiting only. Results showed that the nausea score was higher for the placebo than for the metoclopramide group during the first six hours postoperatively, as was the incidence of retching and vomiting during the following 12 hours. Neither difference, however, was of statistical significance.

In 1973, Dundee, et al., studied 600 adult female patients undergoing minor gynecological procedures of comparable duration utilizing a "standardized anesthetic." No postoperative analgesia was used. The purpose of the study was to test the antiemetic effect of metoclopramide, as well as to evaluate its premedicant capabilities. Only its antiemetic qualities were considered here. Pithidine (100 mgm) was employed to test the antiemetic qualities of metoclopramide since it carries with it a fairly high incidence of sickness when given

within the 90-minute period before operation. Metoclopramide was utilized in either a 10 or 20 mgm dose, being combined with pithidine as a premedicant preparation. When metoclopramide was present in the premedicant, there was no preoperative vomiting; nausea too was decreased in incidence. Postoperatively, vomiting was again less frequent, but nausea was not affected. Total emetic sequelae were significantly reduced in both the first hour after surgery and in the first six hours postoperatively. Considering both parts of the study together, one third of the patients given pithidine vomited either before or after surgery as compared to those receiving pithidine in combination with metoclopramide. One quarter of each group complained of nausea. At the conclusion of the study, the authors suggested that more accurate assessment of the antiemetic value of metoclopramide might involve testing it against 10 mgm of morphine since vomiting was known to occur later and for a longer period of time than with pithidine.

In 1974, a paper describing two additional studies of metoclopramide by Dundee, et al., appeared. The first study utilized 10 and 20 mgm doses of metoclopramide, comparing these doses to the effects of saline or valium for the occurrence of retching, nausea, and vomiting. The subjects were healthy females undergoing minor gynecological operations and the drugs were given as a routine, intramuscular premedicant. There were 100 women in each metoclopramide group, and 200 women in each of the other two groups. Observations were made before surgery at 40, 60 or 90 minutes, or at 60 and 90 minutes after injection. At each observation, both subjective and objective notations were made and noted as slight nausea, marked nausea, or vomiting. The anesthetic technique was standardized. Postoperatively, observations were made at one and six hours utilizing a scoring scheme described by Dundee, Nichol, and Moore in 1962. Occurrences of nausea and/or vomiting were recorded; retching was recorded as

vomiting. No side effects other than complaints of "hunger pains" in the metoclopramide groups were seen preoperatively. Postoperatively, there was a low incidence of emetic sequelae in all groups with no significant difference among the four groups in the six-hour period observed.

The second study involved medical students in their fourth year and was conducted as part of a practical clinical pharmacology class. It did not deal with the antiemetic qualities of metoclopramide and so will not be discussed. The authors concluded that metoclopramide was a safe drug to use in either dose (10 mgm or 20 mgm). Conclusions were drawn from both studies.

Assaf, et al., (1974) performed two studies to determine the efficacy of metoclopramide against emetic symptoms as produced by either morphine 10 mgm, or pithidine 100 mgm. Dundee was one of the investigators involved, and it was he who had suggested this kind of trial after a study of his own in 1973. These two narcotics were chosen for comparison because of their differing rates of onset and durations of action. It is known that pithidine 100 mgm causes more preoperative sickness than morphine 10 mgm, but that morphine 10 mgm lasts longer. Their method of patient selection and evaluation of emetic sequelae in the first study was the same as described in the study by Dundee, et al., in 1974, summarized above. In both groups (the morphine or pithidine) the narcotic was given alone, or in combination with 10 or 20 mgm of metoclopramide as a premedicant preparation, intramuscularly. In the pithidine group of subjects, there were 100 patients in each of three series. The pithidine with metoclopramide 10 mgm was administered in a double-blind fashion. The pithidine with metoclopramide 20 mgm was not given in a double-blind fashion due to the short supply of the concentrated drug, and the necessity of mixing the two drugs. The subsequent mixture was limited to 40 patients. The morphine-metoclopramide group included 40 patients at each dosage level, not administered in a double-

blind manner. These were compared to 100 individuals receiving morphine alone. The anesthetic in all cases was methohexitone, nitrous oxide and oxygen. The metoclopramide was repeated at the end of operation. The control group had received normal saline and was drawn from an earlier study done by the authors. Preoperative vomiting which occurred with fair frequency when pithidine was used, but rarely when morphine was used (considering a 90-minute time period), was completely abolished by either dose of metoclopramide. The effect of metoclopramide on nausea was marked, but it was not absolutely abolished. The beneficial effect of the 20 mgm dose of metoclopramide compared to the 10 mgm dose was marginal with pithidine and absent with morphine. There was a highly significant difference in the incidence of postoperative vomiting at all times when metoclopramide was given with a narcotic as compared to premedication with the narcotic alone, with one exception. The decrease in nausea was much less than for vomiting alone. Consequently, the reduction seen in total emetic sequelae was less than might have been expected. Reviewing both pre- and postoperative emetic sequelae, both doses of metoclopramide resulted in about the same reduction in vomiting and emetic sequelae for pithidine and morphine with slightly lesser efficacy in the six-hour postoperative period for patients who received 10 mgm morphine as their premedicant. The study demonstrated the short duration of the action of metoclopramide since it was much more effective against nausea and vomiting induced by pithidine than that induced by morphine.

The second study in 1974 by Assaf sought to clarify the results of the first study which had been somewhat controversial. In this study, the same two narcotics were utilized as premedicants for women undergoing "standard minor gynecological operations" utilizing a "standard anesthetic"; the exact procedures and anesthetic drugs utilized were not elucidated. The incidence of nausea and vomiting were noted at various intervals during the first six hours postoperatively.

There were 200 women in the morphine group—20 receiving no metoclopramide; 40 receiving 10 mgm of metoclopramide preoperatively; 40 receiving 20 mgm metoclopramide preoperatively; 40 receiving 10 mgm preoperatively and at the end of operation; and 40 receiving 10 mgm of metoclopramide preoperatively and 20 mgm at the end of operation. There were 300 women in the pithidine group—110 receiving no metoclopramide; 100 receiving 10 mgm metoclopramide preoperatively; 40 receiving 20 mgm metoclopramide preoperatively; 20 receiving 10 mgm metoclopramide preoperatively and 10 mgm at the end of operation; and 20 receiving 10 mgm metoclopramide preoperatively and 20 mgm at the end of operation. All medications were given intramuscularly. There was nothing in the results to suggest that 20 mgm of metoclopramide reduced emetic sequelae any more than a 10 mgm dose had. When a second dose of metoclopramide was added at the procedure's end, nausea and vomiting were nearly abolished in the pithidine group postoperatively; the second dose was much less effective in the case of the morphine group. The study confirmed the short duration of metoclopramide.

In 1970, Ellis, et al., conducted a double-blind trial of metoclopramide looking at its sedative and cardiovascular effects in addition to its antiemetic effects. There were 86 healthy women in the trial, comparable by age (19-57), height and weight, and all undergoing minor gynecological surgery. Each woman received 10 mgm of morphine one hour prior to surgery as a premedicant, and each was induced with sodium thiopenthal with cyclopropane and oxygen by mask as the maintenance regime. The women were divided into two groups. One group of 42 women received either 10 mgm of metoclopramide or 1 cc of normal saline, intravenously, just prior to induction with 21 women in each subgroup. In the other group (44), 22 women received 20 mgm of metoclopramide, intravenously pre-induction, the other 22 women receiving 2 cc normal saline intravenously.

Randomization of the ampules in each of the two groups was done through the use of random tables. Identification of the solution used in each case occurred after the one-hour postoperative observation period in the recovery room. Each patient was classified into one of two groups based on postoperative observations—those without any sign of postoperative illness, and those exhibiting nausea, retching or vomiting. Despite the fact that a greater number of women in both control groups experienced postoperative sickness when compared to those who were given metoclopramide, there was no statistical difference between the placebo and metoclopramide groups. The investigators commented that although they realized that a morphine premedicant followed by a cyclopropane anesthetic would present a severe test for determining the antiemetic properties of any drug, they would be reluctant to recommend a drug for use as an antiemetic if it were unable to modify, significantly, the incidence of postoperative anesthetic sickness as was the case in this situation.

Another study examining metoclopramide as an antiemetic was undertaken because the authors felt that previous studies were inconclusive and at considerable variance when results were compared. With this in mind, Shah and Wilson (1972) again looked at a group of women undergoing minor gynecological surgery including dilation and curettage (D and C), cystoscopy, and biopsy of the cervix. The women were randomly allocated to one of two groups--the first receiving metoclopramide 10 mgm, and the second normal saline, intramuscularly, along with the "standard" premedication combination of papavertum 20 mgm and hycosine 0.4 mgm, one hour prior to surgery. The trial drug and placebo ampules were identical, and the contents of the ampule used in each case was unknown to the anesthetist. Anesthetic induction was accomplished with sodium thiopentothal. Maintenance was by mask with halothane, nitrous oxide and oxygen. Occurrence of symptoms—nausea, retching and vomiting, as well as possible side effects (for

example, drowsiness) were noted by nurses for a six-hour postoperative period, and confirmed by the patient the next day through interview. There was no significant difference between the results of the two groups when observing nausea, vomiting and retching. The authors noted the multifactorial etiology of postoperative nausea and vomiting and suggested that the ineffectiveness of metoclopramide in their study might be related to the fact that its central antiemetic effect was so shortlived.

Cook, et al., (1979) compared domperidone, metoclopramide and a placebo for antiemetic effects giving the drugs intravenously just prior to the induction of anesthesia. Identical vials containing either domperidone 4 mgm, metoclopramide 10 mgm or placebo were used in a random fashion. The patients involved in the study were all female undergoing D and C (38), evacuation of the uterus (62), or Cesarean section (CS) (95). All women were A.S.A. Class I or II without known renal, hepatic, central nervous system or cardiac disease. In the women undergoing D and C or uterine evacuation, papavertum was used as the permedicant with anesthesia consisting of a sodium thiopentathol induction and maintenance of halothane, nitrous oxide and oxygen. Women undergoing CS were premedicated with magnesium trisilicate only. Induction was with sodium thiopentothal, intubation was accomplished with succinylcholine, and maintenance of anesthesia utilized nitrous oxide, oxygen and fentanyl. Alcuronium was used for relaxation and was reversed at the end of surgery. The postoperative observation for symptomatology was for 24 hours with periodic visits and assessments occurring during this time. Observations were divided into experiences of nausea only, vomiting, and severe vomiting. Results showed significantly less vomiting with those women undergoing CS when either metoclopramide or domperidone had been given as compared to placebo. No patient experienced nausea alone. Most patients who vomited did so within the first hour after surgery, and none vomited

after the sixth postoperative hour. In the other group of women, those having had either a D and C or uterine evacuation, symptoms were experienced equally by all three drug groups—one exception being severe vomiting in a patient who had received placebo. Overall results of all women considered together showed metoclopramide and domperidone reducing vomiting to approximately the same degree. This reduction reached statistical significance only in those women on whom CS were performed.

In 1979 Kortilla, et al., conducted a study to compare domperidone, droperidol, and metoclopramide in the prevention of nausea and vomiting following a balanced anesthetic. Their population consisted of 185 A.S.A. Class I or II women undergoing elective orthopedic procedures. Domperidone (5-10 mgm), droperidol (1.25 mgm), metoclopramide (10 mgm) or a saline placebo were administered intravenously in a double-blind random fashion five minutes before the end of anesthesia. The same antiemetic was repeated intramuscularly during the first 24 hours postoperatively if the patient complained of nausea, vomiting or retching. If domperidone or metoclopramide were repeated postoperatively, and emesis was still not relieved, droperidol 1.25 mgm was administered intramuscularly at a minimum of 30 minutes after the other drug had been utilized. Incidence of nausea, retching or vomiting for the first 24 hours were monitored at three-hour intervals, and at the end of each interval, a recording of symptoms that occurred was made. Results revealed that only droperidol decreased the incidence of nausea and vomiting when compared with a placebo of saline; domperidone and metoclopramide did not. The incidence of nausea and vomiting in these two groups was similar to that of the control group. Of the patients who received domperidone, metoclopramide or saline, 39-45 percent required an additional dose of the drug while only 22 percent of the droperidol-treated patients needed a repeat dose. In addition, 8-12 percent of the patients requiring

a second dose of metoclopramide, saline or domperidone also required the additional dose of droperidol.

The final study to be considered was conducted by Diamond, et al., in 1980. It was done to evaluate oral metoclopramide as a preoperative antiemetic. The population consisted of two series of patients, one of which was controlled in regard to anesthetic agents and techniques, and the other which had exclusion of narcotics as their only anesthetic entrance criteria. All patients received 20 mgm of metoclopramide or a placebo two hours preoperatively. A double-blind randomized technique was utilized when giving the placebo or metoclopramide, both of which were given orally.

The first group consisted of 104 patients ages 16-60, undergoing orthopedic procedures. They received 0.2 mg/Kg dose of alphaprodine, intravenously, about one half hour before the termination of surgery to present a peripheral and central pharmacological challenge to the antiemetic effect of metoclopramide.

Group two consisted of 102 patients divided equally into orthopedic or abdominal hysterectomy procedures. In recovery room, hydromorphone was given either intravenously or orally upon complaints of pain.

Both groups were observed for nausea, retching or vomiting in three time frame intervals (0-1 hour, 1-3 hours, 3-6 hours). Any incidence of nausea, retching or vomiting was counted as a failure. Reduction in postoperative symptoms was maximal during the 1-3 hour postoperative period, reaching a statistically significant level. On further examination, it appeared that men benefited more from the effects of metoclopramide than did women.

CHAPTER 3

METHODS

Population, Sample and Setting

The population for this study was a convenience (accidental) sample chosen from healthy female adult patients, A.S.A. Class I or II, requiring minor gynecological procedures under general anesthesia with endotracheal intubation in an ambulatory surgery clinic of a hospital in the Atlantic Southeast. Patients were between the ages of 18 and 45.

Thirty patients were selected in a random fashion and assigned to either a control or experimental group using a table prepared by drawing 30 numbers from a container, every other number being placed in the control group—the remaining numbers making up the experimental group. The first five women in the experimental group received metoclopramide 0.15 mgm/Kg of body weight, intravenously, immediately after intubation had been performed. The other ten women in this group received 0.30 mgm/Kg body weight, intravenously, preinduction, at approximately the same time that precurarization was accomplished.

Ages ranged from 21 to 45, with a mean age of 28.2 years. The procedures included one breast biopsy, 13 diagnostic laparoscopies, and 16 laparoscopic tubal ligations. The weights of the women ranged from 36.4 to 94.5 Kg with a mean weight of 65.9 Kg.

Data collection to determine the incidence of nausea, retching, and vomiting in the two groups was performed in the recovery room using a tool designed for this purpose, and at 24 hours postoperatively by phone contact, through direct questioning in an exact manner and sequence in an attempt to eliminate the introduction of suggestion.

Plan of Investigation

Patients were approached the morning of their scheduled surgery at the time of the preanesthetic interview. The purpose of the study was explained, and all questions asked, were answered. The terms nausea, retching, and vomiting were not used in the explanation in order to eliminate suggestion. Rather, the purpose was stated to be to determine if the drug metoclopramide would affect their recovery from surgery and anesthesia. Permission for inclusion into the study was then obtained in accordance with the guidelines of the Committee on the Conduct of Human Research of the institution.

A number 18 jelco catheter was placed and secured being occluded with the appropriate obturator until the time of surgery. At that time, patients were accompanied to the surgical suite and assisted in positioning themselves on the operating room table. An intravenous solution of five percent dextrose in lactated ringers was then connected to the jelco catheter for the induction and maintenance of anesthesia.

A rapid sequence induction was utilized to facilitate rapid intubation and to reduce the probability of introducing gas into the stomach. Reduction of the probability of gas entering the stomach was desired to decrease the likelihood of gastric distention and therefore eliminate one possible cause for postoperative nausea, retching, and vomiting.

Induction proceeded as follows:

1. Preoxygenation with 100 percent oxygen for three to five minutes.
2. Pretreatment with d-tubocurarine 0.04 mgm/Kg intravenously at least three minutes prior to the administration of succinylcholine.
3. Succinylcholine 1.5 mgm/Kg intravenously for intubation.
4. Sodium brevitall 1 mgm/Kg intravenously immediately following the succinylcholine, with the intravenous fluid running quickly to prevent drug mixing in the tubing.

5. Patients were not assisted with ventilation in order to prevent the introduction of gas into the stomach. Patients were observed for ventilatory effort cessation.
6. Approximately 90 seconds after the infusion of the succinylcholine and sodium breivital, and after muscle relaxation had been confirmed by means of a peripheral nerve stimulator, endotracheal intubation was accomplished within 40 seconds under direct vision laryngoscopy using a number three Miller blade. A cuffed endotracheal tube, size 7.0 mm, was used.
7. The cuff was inflated prior to assisting ventilation.
Maintenance of anesthesia included:
 1. Fentanyl 2 ug/Kg intravenously was given after the endotracheal tube had been successfully placed.
 2. Nitrous oxide and oxygen in 70/30 proportions were added after successful intubation.
 3. Isoflurane in concentrations no greater than one percent were added as necessary to supplement the above agents.
 4. A succinylcholine drip, 0.2 percent, was used to provide sufficient muscle relaxation as needed. It was given through intravenous titration and its total dose never exceeded 7 mgm/Kg body weight.

Data Collection

Observation for and recording of the occurrence and frequency of nausea, retching and vomiting began upon the patient's arrival to the recovery room using the tool provided. Observation by recovery room personnel or by the investigator continued throughout the patient's stay and ceased only upon their discharge home. Patients were asked to continue self-observation for any problems in their recovery until the next morning when contact by telephone was made. At this

time, patients were carefully questioned about the occurrence of postoperative problems after their discharge from the ambulatory surgery clinic. Questions progressed from general to specific to avoid the suggestion of symptoms in which the study was interested. The symptoms of nausea, retching and vomiting were again recorded on the tool when they were verbalized as having occurred by the patient.

Complete confidentiality was maintained during this research study. Names of the individuals included were not used, and data collection, in addition to observations made concerning nausea, retching and vomiting included patient age, sex and weight, and dosages of the drugs utilized. Length of recovery room stay, in minutes, was also collected.

The independent variable (metoclopramide administration) was measured nominally, the patient groups being categorized according to whether drug intervention had been utilized or not.

Instrumentation

The dependent variables (postoperative nausea, retching and vomiting) were measured through the use of a simple checklist tool. An example of the tool is included in the appendix. The subjective symptom, nausea, was noted as being either spontaneously voiced, or as elicited (for example--being voiced only after being asked "how do you feel?"). The word "nausea" was never used in questioning to avoid its introduction through suggestion. Within either category, it was noted on a Likert-type scale in an attempt to further qualify the symptom once it had been voiced. All three symptoms were noted at each occurrence, the time being recorded as well as the event. The tool was explained to recovery room personnel prior to beginning the study, and questions were encouraged. The investigator was present during data collection in most instances.

At the 24-hour point, patients were contacted by phone. Questioning was begun in a general fashion, progressing to specific symptomatology. Again, nausea was ranked according to a Likert-type scale. Notations were made on the reverse of the recovery room tool.

Data Analysis

This study was interested in the presence or absence of symptoms (nausea, retching and vomiting) within the treatment groups studied. The Fisher Exact test was used to compare the three treatment groups with respect to the presence or absence of these symptoms, when the properties in question were arranged to compare two classifications for each of two variables. In this case, two treatment groups were compared at a time, as either having experienced or not experienced, a given symptom—thus giving a two-by-two contingency table. The test allowed for the acceptance or rejection of the null hypothesis that there was no difference between the two treatment groups in question when considering whether a given symptom did or did not occur. (Mosteller, 1970) The chi square test was inappropriate for use in this case because the expected cell counts were too small. The Fisher test was a test developed for use in such an event to prevent a Type I error (rejection of the null hypothesis when it should not be rejected). (Bhattacharyya, 1977) (Mosteller, 1970) (Polit, 1978)

Since the patients involved were discharged home from the recovery room as soon as the majority of the effects of anesthesia had worn off, they were without the assistance of medical personnel should problems encountered in the recovery room recur once home. In the triad of symptoms studied vomiting, in particular, can be of real concern since if persistent can lead to dehydration, electrolyte depletion, further vomiting, as well as other physiological imbalances. With this in mind, the three symptoms were analyzed to determine if their

occurrence had varied at the 24-hour period as compared to their occurrence in the recovery room. The three treatment groups were also compared to see if one group or another showed a difference in the symptoms that were experienced at the two different time frames. A symptom was noted as having occurred (yes) or as not having occurred (no). FUNCAT was the analysis technique used because it allowed the appropriate statistical analysis when the responses were categorical in nature. In this case, the response was binary—either yes or no, within a given treatment group.

One of the important qualities an antiemetic must possess in order to be used in an outpatient surgical setting is the ability to work effectively without extending the length of the recovery room stay required by the patient. A nonparametric test, the Kruskal-Wallis test, was used to compare the median lengths of stay for the three treatment groups. This test was based on the assignment of ranks to the scores (recovery room stay in minutes) of the three treatment groups. (Polit, 1978) Since ties were found within the ranked data, an adjusted test, the Kruskal-Wallis statistic H was finally used to analyze the data. (Bhattacharyya, 1977) The resulting analysis allowed the acceptance or rejection of the null hypothesis that there was no difference in the median length of stays for the three dosage groups.

CHAPTER 4

RESULTS

Introduction

This portion of the paper presents a summary of the results, raw data with statistical values, and summary of table contents.

Summary of Results

Comparing the drug-treated subjects (both groups together) with those receiving no drug, there was no significant difference in the occurrence of any of the symptoms--nausea, retching or vomiting--in either the recovery room setting or at the 24-hour home call time frame. The two drug groups were considered together for statistical purposes, since when considered separately there were no differences found. (Tables 8-14)

When each of the treated groups were considered separately at both the recovery room and 24-hour time frames for each of the symptoms of interest (nausea, retching and vomiting), there was essentially no significant difference in the occurrence of symptoms when either the treatment or the two time frames were compared. The one exception was for the symptom vomiting, which occurred at only a marginally less level of significance than either of the other two symptoms when looking at both treatment regimes and time frames ($p=0.0585$). (Tables 15-17)

Addressing median lengths of stay in the recovery room for the three groups, there was no significant difference in the required recovery room stays among the three groups. (Table 18)

TABLE 1: The Occurrence of Spontaneous Nausea in the Recovery Room

OCCURRENCE	CONTROL	.15 MGM	.30 MGM
None	13 86.67%	3 60.00%	7 70.00%
Slight	0 0.00%	0 0.00%	1 10.00%
Moderate	1 6.67%	1 20.00%	2 20.00%
Severe	1 6.67%	1 20.00%	0 0.00%
Total	15	5	10

TABLE 2: The Occurrence of Elicited Nausea in the Recovery Room

OCCURRENCE	CONTROL	.15 MGM	.30 MGM
None	14 93.33%	4 80.00%	10 100.00%
Slight	1 6.67%	1 20.00%	0 0.00%
Total	15	5	10

TABLE 3: The Occurrence of Retching in the Recovery Room

OCCURRENCE	CONTROL	.15 MGM	.30 MGM
No	13 86.67%	4 80.00%	10 100.00%
Yes	2 13.33%	1 20.00%	0 0.00%
Total	15	5	10

TABLE 4: The Occurrence of Vomiting in the Recovery Room

OCCURRENCE	CONTROL	.15 MGM	.30 MGM
No	11 73.33%	3 60.00%	7 70.00%
Once	4 26.67%	1 20.00%	2 20.00%
More than Once	0 0.00%	1 20.00%	1 10.00%
Total	15	5	10

TABLE 5: The Occurrence of Nausea at 24 Hours

OCCURRENCE	CONTROL	.15 MGM	.30 MGM
None	9 60.00%	1 20.00%	8 80.00%
Slight	5 33.33%	2 40.00%	1 10.00%
Moderate	1 6.67%	1 20.00%	1 10.00%
Unable To Reach	0 0.00%	1 20.00%	0 0.00%
Total	15	5	10

TABLE 6: The Occurrence of Retching at 24 Hours

OCCURRENCE	CONTROL	.15 MGM	.30 MGM
No	12 80.00%	2 40.00%	10 100.00%
Yes	3 20.00%	2 40.00%	0 0.00%
Unable To Reach	0 0.00%	1 20.00%	0 0.00%
Total	15	5	10

TABLE 7: The Occurrence of Vomiting at 24 Hours

OCCURRENCE	CONTROL	.15 MGM	.30 MGM
No	11 73.33%	0 0.00%	9 90.00%
Once	1 6.67%	1 20.00%	0 0.00%
More Than Once	3 20.00%	3 60.00%	1 10.00%
Unable To Reach	0 0.00%	1 20.00%	0 0.00%
Total	15	5	10

TABLE 8: 2x2 Contingency Table for Spontaneous Nausea in the Recovery Room

OCCURRENCE	CONTROL	DRUG	TOTAL
None	13 86.67%	10 66.67%	23
Some	2 13.33%	5 33.33%	7
Total	15	15	30

Fisher's Exact
Test P=0.3898

TABLE 9: 2x2 Contingency Table for Elicited Nausea in the Recovery Room

OCCURRENCE	CONTROL	DRUG	TOTAL
None	14 93.33%	14 93.33%	28
Some	1 6.67%	1 6.67%	2
Total	15	15	30

Fisher's Exact
Test P=1.0000

TABLE 10: 2x2 Contingency Table for Retching in the Recovery Room

OCCURRENCE	CONTROL	DRUG	TOTAL
No	13 86.67%	14 93.33%	27
Yes	2 13.33%	1 6.67%	3
Total	15	15	30

Fisher's Exact
Test P=1.0000

TABLE 11: 2x2 Contingency Table for Vomiting in the Recovery Room

OCCURRENCE	CONTROL	DRUG	TOTAL
No	11 73.33%	10 66.67%	21
Once or More	4 26.67%	5 33.33%	9
Total	15	15	30

Fisher's Exact
Test P=1.0000

TABLE 12: 2x2 Contingency Table for Nausea at 24 Hours

OCCURRENCE	CONTROL	DRUG	TOTAL
None	9 60.00%	9 64.29%	18
Some	6 40.00%	5 35.71%	11
Total	15	14	29

Fisher's Exact
Test P=1.000

TABLE 13: 2x2 Contingency Table for Retching at 24 Hours

OCCURRENCE	CONTROL	DRUG	TOTAL
No	12 80.00%	12 85.71%	24
Yes	3 20.00%	2 14.29%	5
Total	15	14	29

Fisher's Exact
Test P=1.0000

TABLE 14: 2x2 Contingency Table for Vomiting at 24 Hours

OCCURRENCE	CONTROL	DRUG	TOTAL
No	11 73.33%	9 64.29%	20
Once or More	4 26.67%	5 35.71%	9
Total	15	14	29

Fisher's Exact
Test P=0.6999

TABLE 15A & B: FUNCAT Analysis Evaluating the Occurrence of Nausea Between the Three Treatment Groups in the Recovery Room Compared to 24 Hours

A

One Way Frequency Table		
Variable	Value	Count
Nausea	No	39
	Yes	19
Dose	Control	30
	.15 mgm	8
	.30 mgm	20
Time	RR*	29
	24**	29

Dose: P=0.1733

B

Response Frequencies for Nausea			
Dose	Time	Nausea -No-	Nausea -Yes-
Control	RR*	12	3
	24**	9	6
.15 mgm	RR*	2	2
	24**	1	3
.30 mgm	RR*	7	3
	24**	8	2

Time: P=0.4484

TABLE 16A & B: FUNCAT Analysis Evaluating the Occurrence of Retching Between the Three Treatment Groups in the Recovery Room Compared to 24 Hours

A

One Way Frequency Table		
Variable	Value	Count
Retching	No	50
	Yes	8
Dose	Control	30
	.15 mgm	8
	.30 mgm	20
Time	RR*	29
	24**	29

Dose: P=0.1547

B

Response Frequencies for Retching			
Dose	Time	Retching -No-	Retching -Yes-
Control	RR*	13	2
	24**	12	3
.15 mgm	RR*	3	1
	24**	2	2
.30 mgm	RR*	10	0
	24**	10	0

Time: P=0.5637

TABLE 17A & B: FUNCAT Analysis Evaluating the Occurrence of Vomiting Between the Three Treatment Groups in the Recovery Room Compared to 24 Hours

A

One Way Frequency Table		
Variable	Value	Count
Vomiting	No	40
	Yes	18
Dose	Control	30
	.15 mgm	8
	.30 mgm	20
Time	RR*	29
	24**	29

Dose: P=0.0585

B

Response Frequencies for Vomiting			
Dose	Time	Vomiting -No-	Vomiting -Yes-
Control	RR*	11	4
	24**	11	4
.15 mgm	RR*	2	2
	24**	0	4
.30 mgm	RR*	7	3
	24**	9	1

Time: P=0.7562

*RR = Recovery Room

**24 = 24 hours

TABLE 18: Comparison of Length of Recovery Room Stays for the Three Dosage Groups Using Ranked Values

*Control	Ranked Values	*.15 mgm	Ranked Values	*.30 mgm	Ranked Values
85	10.5	65	3.0	90	15.0
60	1.5	90	15.0	79	6.0
95	17.5	150	29.0	129	27.0
90	15.0	102	22.0	85	10.5
85	10.5	125	26.0	135	28.0
118	25.0			85	10.5
95	17.5			75	4.5
215	30.0			85	10.5
60	1.5			80	7.0
85	10.5			110	24.0
100	20.0				
100	20.0				
75	4.5				
100	20.0				
105	23.0				

*Time in each treatment group is in minutes

Control: $R=227 (R_1)$

.15 mgm: $R=95 (R_2)$

.30 mgm: $R=143 (R_3)$

$P(H \geq 1.01069)=0.6033$: Kruskal-Wallis Test Statistic H

SUMMARY OF TABLE CONTENTS

TABLE 1: The Occurrence of Spontaneous Nausea in the Recovery Room

Control: N=15

None: N=13(86.67%) Slight: N=0(0.00%) Moderate: N=1(6.67%)

Severe: N=1(6.67%)

.15 mgm/kgm: N=5

None: N=3(60.00%) Slight: N=0(0.00%) Moderate: N=1(20.00%)

Severe: N=1(20.00%)

.30 mgm/kgm: N=10

None: N=7(70.00%) Slight: N=1(10.00%) Moderate: N=2(20.00%)

Severe: N=0(0.00%)

TABLE 2: The Occurrence of Elicited Nausea in the Recovery Room

Control: N=15

None: N=14(93.33%) Slight: N=1(6.67%)

.15 mgm/kgm: N=5

None: N=4(80.00%) Slight: N=1(20.00%)

.30 mgm/kgm: N=10

None: N=10(100.00%) Slight: N=0(0.00%)

TABLE 3: The Occurrence of Retching in the Recovery Room

Control: N=15

No: N=13(86.67%) Yes: N=2(13.33%)

.15 mgm/kgm: N=5

No: N=4(80.00%) Yes: N=1(20.00%)

.30 mgm/kgm: N=10

No: N=10(100.00%) Yes: N=0(0.00%)

TABLE 4: The Occurrence of Vomiting in the Recovery Room

Control: N=15

No: N=11(73.33%) Once: N=4(26.67%)

More Than Once: N=0(0.00%)

.15 mgm/kgm: N=5

No: N=3(60.00%) Once: N=1(20.00%)

More Than Once: N=1(20.00%)

.30 mgm/kgm: N=10

No: N=7(70.00%) Once: N=2(20.00%)

More Than Once: N=1(10.00%)

TABLE 5: The Occurrence of Nausea at 24 Hours

Control: N=15
None: N=9(60.00%) Slight: N=5(33.33%) Moderate: N=1(6.67%)
Unable to Reach: N=0(0.00%)
.15 mgm/kgm: N=5
None: N=1(20.00%) Slight: N=2(40.00%) Moderate: N=1(20.00%)
Unable to Reach: N=1(20.00%)
.30 mgm/kgm: N=10
None: N=8(80.00%) Slight: N=1(10.00%) Moderate: N=1(10.00%)
Unable to Reach: N=0(0.00%)

TABLE 6: The Occurrence of Retching at 24 Hours

Control: N=15
No: N=12(80.00%) Yes: N=3(20.00%)
Unable to Reach: N=0(0.00%)
.15 mgm/kgm: N=5
No: N=2(40.00%) Yes: N=2(40.00%) Unable to Reach: N=1(20.00%)
.30 mgm/kgm: N=10
No: N=10(100.00%) Yes: N=0(0.00%) Unable to Reach: N=0(0.00%)

TABLE 7: The Occurrence of Vomiting at 24 Hours

Control: N=15
No: N=11(73.33%) Once: N=1(6.67%) More Than Once: N=3(20.00%)
Unable to Reach: N=0(0.00%)
.15 mgm/kgm: N=5
No: N=0(0.00%) Once: N=1(20.00%) More Than Once: N=3(60.00%)
Unable to Reach: N=1(20.00%)
.30 mgm/kgm: N=10
No: N=9(90.00%) Once: N=0(0.00%) More Than Once: N=1(10.00%)
Unable to Reach: N=0(0.00%)

TABLE 8: 2x2 Contingency Table for Spontaneous Nausea in the Recovery Room

Control: N=15
None: N=13(86.67%) Some: N=2(13.36%)
Drug: N=15
None: N=10(66.67%) Some: N=5(33.33%)
Total: N=30
Control: N=15 Drug: N=15 None: N=23 Some: N=7
Fisher's Exact Test: P=0.3898

Based on the result of the Fisher's Exact Test, there is not sufficient evidence to reject the null hypothesis of no difference between the two treatment groups when looking at the incidence of spontaneous nausea in the recovery room.

TABLE 9: 2x2 Contingency Table for Elicited Nausea in the Recovery Room

Control: N=15

None: N=14(93.33%) Some: N=1(6.67%)

Drug: N=15

None: N=14(93.33%) Some: N=1(6.67%)

Total: N=30

Control: N=15 Drug: N=15 None: N=28 Some: N=2

Fisher's Exact Test: P=1.0000

Based on the result of the Fisher's Exact Test, there is not sufficient evidence to reject the null hypothesis of no difference between the two treatment groups when looking at the incidence of elicited nausea in the recovery room.

TABLE 10: 2x2 Contingency Table for Retching in the Recovery Room

Control: N=15

No: N=13(86.67%) Yes: N=2(13.33%)

Drug: N=15

No: N=14(93.33%) Yes: N=1(6.67%)

Total: N=30

Control: N=15 Drug: N=15 No: N=27 Yes: N=3

Fisher's Exact Test: P=1.0000

Based on the result of the Fisher's Exact Test, there is not sufficient evidence to reject the null hypothesis of no difference between the two treatment groups when looking at the incidence of retching in the recovery room.

TABLE 11: 2x2 Contingency Table for Vomiting in the Recovery Room

Control: N=15

No: N=11(73.33%) Once or More: N=4(26.67%)

Drug: N=15

No: N=10(66.67%) Once or More: N=5(33.33%)

Total: N=30

Control: N=15 Drug: N=15 No: N=21 Once or More: N=9

Fisher's Exact Test: P=1.0000

Based on the result of the Fisher's Exact Test, there is not sufficient evidence to reject the null hypothesis of no difference between the two treatment groups when looking at the incidence of vomiting in the recovery room.

TABLE 12: 2x2 Contingency Table for Nausea at 24 Hours

Control: N=15

None: N=9(60.00%) Some: N=6(40.00%)

Drug: N=14

None: N=9(64.29%) Some: N=5(35.71%)

Total: N=29

Control: N=15 Drug: N=14 None: N=18 Some: N=11

Fisher's Exact Test: P=1.0000

Based on the result of the Fisher's Exact Test, there is not sufficient evidence to reject the null hypothesis of no difference between the two treatment groups when looking at the incidence of nausea at 24 hours.

TABLE 13: 2x2 Contingency Table for Retching at 24 Hours

Control: N=15

No: N=12(80.00%) Yes: N=3(20.00%)

Drug: N=14

No: N=12(85.71%) Yes: N=2(14.29%)

Total: N=29

Control: N=15 Drug: N=14 No: N=24 Yes: N=5

Fisher's Exact Test: P=1.0000

Based on the result of the Fisher's Exact Test, there is not sufficient evidence to reject the null hypothesis of no difference between the two treatment groups when looking at the incidence of retching at 24 hours.

TABLE 14: 2x2 Contingency Table for Vomiting at 24 Hours

Control: N=15

No: N=11(73.33%) Once or More: N=4(26.67%)

Drug: N=14

No: N=9(64.29%) Once or More: N=5(35.71%)

Total: N=29

Control: N=15 Drug: N=14 No: N=20 Once or More: N=9

Fisher's Exact Test: P=0.6999

Based on the result of the Fisher's Exact Test, there is not sufficient evidence to reject the null hypothesis of no difference between the two treatment groups when looking at the incidence of vomiting at 24 hours.

**TABLE 15: Funcat Analysis Evaluating the Occurrence of Nausea
Between the Three Treatment Groups in the Recovery Room
Compared to 24 Hours**

A-One Way Frequency Table

Variable: Nausea

Value: No; N=39 Value: Yes; N=39

Variable: Dose

Value: Control; N=30

Value: .15 mgm; N=8

Value: .30 mgm; N=20

Variable: Time

Value: Recovery Room; N=29

Value: 24 Hours; N=29

B-Response Frequencies for Nausea

Dose: Control

Time: Recovery Room Nausea; No: N=12 Yes: N=3

Time: 24 hours Nausea; No: N=9 Yes: N=6

Dose: .15 mgm

Time: Recovery Room Nausea; No: N=2 Yes: N=2

Time: 24 hours Nausea; No: N=1 Yes: N=3

Dose: .30 mgm

Time: Recovery Room Nausea; No: N=7 Yes: N=3

Time: 24 hours Nausea; No: N=8 Yes: N=2

FUNCAT Analysis, Dose: P=0.1733

Based on the result of the FUNCAT procedure, there is not sufficient evidence to reject the null hypothesis of no difference between the three treatment groups when looking at nausea.

FUNCAT Analysis, Time: P=0.4484

Based on the result of the FUNCAT procedure, there is not sufficient evidence to reject the null hypothesis of no difference between the two time frames when looking at nausea.

TABLE 16: Funcat Analysis Evaluating the Occurrence of Retching Between the Three Treatment Groups in the Recovery Room Compared to 24 Hours

A-One Way Frequency Table

Variable: Retching

Value: No; N=50 Value: Yes; N=8

Variable: Dose

Value: Control; N=30

Value: .15 mgm; N=8

Value: .30 mgm; N=20

Variable: Time

Value: Recovery Room; N=29

Value: 24 Hours; N=29

B-Response Frequencies for Retching

Dose: Control

Time: Recovery Room Retching; No: N=13 Yes: N=2

Time: 24 hours Retching; No: N=12 Yes: N=3

Dose: .15 mgm

Time: Recovery Room Retching; No: N=3 Yes: N=1

Time: 24 hours Retching; No: N=2 Yes: N=2

Dose: .30 mgm

Time: Recovery Room Retching; No: N=10 Yes: N=0

Time: 24 hours Retching; No: N=10 Yes: N=0

FUNCAT Analysis, Dose: $P=0.1547$

Based on the result of the FUNCAT procedure, there is not sufficient evidence to reject the null hypothesis of no difference between the three treatment groups when looking at retching.

FUNCAT Analysis, Time: $P=0.5637$

Based on the result of the FUNCAT procedure, there is not sufficient evidence to reject the null hypothesis of no difference between the two time frames when looking at retching.

TABLE 17: Funcat Analysis Evaluating the Occurrence of Vomiting Between the Three Treatment Groups in the Recovery Room Compared to 24 Hours

A-One Way Frequency Table

Variable: Vomiting

Value: No; N=40 Value: Yes; N=18

Variable: Dose

Value: Control; N=30

Value: .15 mgm; N=8

Value: .30 mgm; N=20

Variable: Time

Value: Recovery Room; N=29

Value: 24 Hours; N=29

B-Response Frequencies for Vomiting

Dose: Control

Time: Recovery Room Vomiting; No: N=11 Yes: N=14

Time: 24 hours Vomiting; No: N=11 Yes: N=4

Dose: .15 mgm

Time: Recovery Room Vomiting; No: N=2 Yes: N=2

Time: 24 hours Vomiting; No: N=0 Yes: N=4

Dose: .30 mgm

Time: Recovery Room Vomiting; No: N=7 Yes: N=3

Time: 24 hours Vomiting; No: N=9 Yes: N=1

FUNCAT Analysis, Dose: $P=0.0585$

Based on the result of the FUNCAT procedure, there is not sufficient evidence to reject the null hypothesis of no difference between the three treatment groups when looking at vomiting.

FUNCAT Analysis, Dose: $P=0.7562$

Based on the result of the FUNCAT procedure, there is not sufficient evidence to reject the null hypothesis of no difference between the two time frames when looking at vomiting.

TABLE 18: Comparison of Length of Recovery Room Stays for the Three Dosage Groups using Ranked Values

Control: N=15

Recovery Room stay in minutes: Minimum - 60 min.
Maximum - 215 min.

Sum of Ranked Values: $R=227 (R_1)$

.15 mgm: N=5

Recovery Room stay in minutes: Minimum - 65 min.
Maximum - 150 min.

Sum of Ranked Values: $R=95 (R_2)$

.30 mgm: N=10

Recovery Room stay in minutes: Minimum - 75 min.
Maximum - 135 min.

Sum of Ranked Values: $R=143 (R_3)$

Kruskal-Wallis Test Statistic H: $P(H' \geq 1.01069)=0.6033$

Based on the results of the Kruskal-Wallis Test Statistic 'H,' there is not sufficient evidence to reject the null hypothesis of no difference in the median length of recovery room stays for the three dosage groups.

CHAPTER 5

DISCUSSION

Based on the results of this study, metoclopramide offered no protection against the postoperative symptoms of nausea, retching and vomiting when compared to a control group receiving no medication, when utilized in an ambulatory surgical setting in conjunction with general anesthesia and endotracheal intubation. The population consisted of 30 women, A.S.A. Class I or II, undergoing minor gynecological procedures. In only one instance was there a marginally significant difference in the occurrence of a symptom and this was for the symptom of vomiting. When comparing the time frames in the three treatment groups, vomiting occurred marginally less frequently than the other two symptoms in looking at treatment and time ($p=0.0585$).

Narcotics are known to cause the symptomatology of nausea, retching, and vomiting through a central effect. It was proposed that since narcotics were utilized in the outpatient setting in which this study was conducted—metoclopramide—also working centrally, might reduce these symptoms and therefore be of benefit in the ambulatory surgical setting where quick recovery is a necessity. Though symptomatology was not affected in this study, neither was recovery, the drug groups required no increased time of stay in the recovery room when compared to the untreated group. Since metoclopramide speeds gastric emptying in addition to its central antiemetic effect, and the ambulatory surgery situation is an area where an empty stomach can never be guaranteed, this is seen as an added benefit when the potential for vomiting and aspiration is considered. With this in mind, it is suggested that metoclopramide might be tested in this situation but in a higher dosage level, since it appears to have many of the qualities desirable in the ambulatory surgical setting.

In the majority of cases evaluated here (29 out of 30), the abdomen was filled with gas in order to visualize the structures of interest (fallopian tubes, ovaries, and uterus) when laparoscopy was performed. It is suggested that filling the abdominal cavity with gas, thereby placing pressure on the abdominal contents, might cause an increase in the incidence of the symptoms of interest. If this is a possibility, then the dose of metoclopramide may need to be increased to counteract this parameter influencing the postoperative occurrence of nausea, retching and vomiting. Since the doses involved in this study did not increase recovery room stays, an increase in the dosages of metoclopramide is not seen as an unrealistic recommendation.

Shah and Wilson (1972) looked at women undergoing minor gynecological procedures (D and C, cytoscopy, and biopsy of the cervix). The narcotics utilized were given preoperatively in a combination of papavertum 20 mgm and hycosine 0.4 mgm along with either metoclopramide 10 mgm or normal saline. Induction was with sodium thiopentothal, and maintenance of anesthesia was accomplished using halothane, nitrous oxide, and oxygen. The symptomatology of nausea, retching, and vomiting were again evaluated, but only for a six-hour posoperative period. Their study, as this one, revealed no significant difference between the group receiving metoclopramide as compared to the group receiving placebo.

In a study by Assaf (1974), women undergoing minor gynecological procedures were studied. Narcotics were utilized in the preoperative medication, either with or without metoclopramide. The metoclopramide was used in two dosage strengths—10 mgm or 20 mgm. In addition, in some cases, the metoclopramide was repeated at the end of operation. Though neither dosage of metoclopramide was found to be more effective than the other in reducing emetic sequelae, it was noted that when a second dose of metoclopramide was utilized at the end of the surgical procedure, nausea and vomiting were almost completely abolished

when pithidine was the preoperative narcotic used. Emetic sequelae in the morphine group were not reduced as much, probably attributable to its longer duration. Since metoclopramide is short acting, and the narcotics in the ambulatory setting must of necessity be of short duration (usually fentanyl), it is suggested that metoclopramide be studied in this setting, the dose being divided, the first half being given intravenously as anesthesia is induced, and the other half through intramuscular injections at the end of the surgical procedure, just prior to emergence. This may provide greater protection against nausea, retching and vomiting in the postoperative period, extending even beyond discharge when medical intervention is not available.

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APPENDIX

EXPLANATION OF WHAT IS TO BE PERFORMED

(Consent Form)

The purpose of this study is to determine if the drug metoclopramide affects your recovery from surgery and anesthesia. Metoclopramide is a very effective drug with few side effects.

You will randomly be assigned to one of two groups:

Group 1 will receive metoclopramide intravenously with the anesthetic drugs.

Group 2 will not receive metoclopramide with the anesthetic drugs.

You will be unaware of which group you are in.

The anesthetic induction (process of going to sleep) will be performed routinely in a manner such that gastric distention (filling of the stomach with gas) with anesthetic gases will be minimized. Your anesthetic management will proceed in the same manner whether or not you choose to participate in the study.

You will be monitored in the recovery room until your discharge for the pleasantness of your recovery. You will also be contacted by phone sometime during the day after your surgery to see if you have experienced any problems since your discharge.

The side effects of metoclopramide which may or may not occur are usually mild and transient and may include drowsiness, lassitude or faintness, and bowel disturbances.

The results of this study will enable us to evaluate the potential for metoclopramide towards providing a smoother, safer recovery from surgery and anesthesia.

Initials

Date

HOME CALL QUESTIONNAIRE

Patients will be contacted as soon as possible the day after surgery regarding their recovery once they were discharged. Questions will proceed from general to specific, leaving the subjective symptom "nausea" until last to eliminate as much suggestive input as possible. If "nausea" is mentioned as an event that occurred, either spontaneously or from questioning, it will be noted as slight, moderate, or severe through the three qualifying statements indicated below.

1. How was your recovery from your surgery once you were home?
2. Did you experience any vomiting?
3. Did you experience any retching?
4. Did you experience any nausea? If the answer is yes:

Present, but not enough to be considered troublesome (slight)

Present, and enough to be unpleasant (moderate)

Present, and enough to be unpleasant and interfered with other activities (severe)

5. Have you ever experienced retching, vomiting or nausea after other surgeries you have had?

POSTANESTHETIC RECOVERY ROOM RECORD

Demographic Information

Surgical Procedure:

Age:

Weight:

Telephone No.:

Length of Anesthesia:

Intraoperative Medications Utilized:

Time of Metoclopramide Administration:

Dose of Metoclopramide:

Date/Time of Arrival:

Time of Discharge:

<u>NAUSEA</u>							<u>RETCHING</u>	<u>VOMITING</u>
time	spon. sl. mod. sev.			elict. sl. mod. sev.				

Key: spon. - spontaneous; elict. - elicited; sl. - slight; mod. - moderate;
sev. - severe

Retching and vomiting are objective events and should be recorded when observed. Note the time they occurred and check the appropriate event. **Nausea is a subjective event.** As such, it should be identified as a spontaneous event (the patient voices its occurrence without prompting), or an elicited event (the patient voices its occurrence upon questioning). In questioning, avoid use of the word "nausea"; use general questions such as "how do you feel?". If nausea does occur, either as an elicited or a spontaneous event, please qualify the symptom as slight, moderate, or severe through further questions.

RESEARCH VOLUNTEER AGREEMENT

I, _____, having attained my 18th birthday, and otherwise having full capacity to consent, do hereby volunteer to participate in a research study entitled: "THE EFFECT OF METACLOPRAMIDE ON POSTOPERATIVE RECOVERY FROM SURGERY AND GENERAL ANESTHESIA" under the direction of _____.

The implications of my voluntary participation; the nature, duration and purpose; the methods and means by which it is to be conducted; and the inconveniences and hazards to be expected have been thoroughly explained to me by _____, and are set forth in full in this Agreement, which I have initialed. I have been given an opportunity to ask questions concerning this research study, and any such questions have been answered to my full and complete satisfaction.

I understand that I may at any time during the course of this research study revoke my consent and withdraw from the study without prejudice. I understand that in the event of my withdrawal or termination, the attending physicians may find it necessary for me to undergo certain further examinations if, in the opinion of the attending physician, such examinations are necessary for my health or well being.

Pregnancy will be cause for exclusion from the study.

I agree that the information obtained from this study may be used for teaching or for publication in scientific literature. My name and identity will be kept confidential.

I understand that in the event of any physical and/or mental injury resulting from my participation in this research project, Virginia Commonwealth University will not offer compensation or medical treatment.

Signature

Date

I was present during the explanation referred to the above, as well as the volunteer's opportunity for questions and hereby witness his signature.

Signature

Date

VITA

Kay Ann Prather was born on May 26, 1941, in Kingman County, Kansas, and is an American citizen. She graduated from Earl Warren Senior High School, Downey, California, in 1959. She received her Registered Nurse Diploma from California Hospital School of Nursing, Los Angeles, California, in 1964. She received her certification as a Registered Nurse Anesthetist from the School of Nurse Anesthesia, Wilford Hall Medical Center, United States Air Force, San Antonio, Texas, in 1978. She received her Bachelor of Science in Nursing from Saint Louis University, Saint Louis, Missouri, in 1981.

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